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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,171	03/19/2004	Mark G. Erlander	022041-001110US	7392

41578 7590 11/01/2005

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,171	ERLANDER ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/3/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Regarding Claim 8, and any claims dependent thereof, the language "...said DNA polymerase activity is DNA dependent..." fails to further limit the subject matter of the parent claim because the use of a DNA-dependent DNA polymerase is *required* for the step of producing ds-cDNA set forth in the instant reaction conditions. Claim 9 identifies *specific* DNA-dependent polymerase activities thereby properly limiting the subject matter of the parent claim, however, remains objected to due to its dependence on claim 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 2, 4-9, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (WO 99/25873).

Regarding Claim 1, Wang et al. disclose a method for unbiased RNA amplification (Figures 1, 2; Page 6, Line 31-Column 12 Line 5; Page 15, Line 20-Page 19, Line 17, for example) comprising: a) forming double stranded cDNA templates containing sequences present in said target polynucleotide, wherein said sequences are operably linked to a promoter, by i) annealing said single stranded target polynucleotide with a plurality of first oligonucleotides, each comprising a random primer sequence ("region of arbitrary sequence", Page 4 Lines 31,32), to form a first complex, ii) synthesizing a first strand cDNA by reverse transcription of said first complex (Page 7, Lines 30,31, for example) and adding a homopolymer tail to said first strand cDNA by use of terminal deoxyribonucleotidyl transferase activity (Page 8, Lines 8-11), iii) optionally degrading first oligonucleotides not used in i) or ii) above with exonuclease activity (Limitation not addressed because it is optional), iv) annealing said first strand cDNA, after denaturing the mRNA/cDNA hybrid or degrading the RNA from said hybrid, with a second polynucleotide comprising a primer sequence, complementary to said homopolymer tail and operably linked to a promoter region (Page 8, Lines 8-11), to form a population of second complexes, and v) forming double stranded cDNA templates from said population of second complexes with DNA polymerase activity (Page 7, Line 30-Page 8, Line 11; Page 16, Lines 5-14, for example); and b) transcribing said cDNA templates with an RNA polymerase capable of initiating transcription via said promoter

region to produce amplified RNA (aRNA) containing sequences of said target polynucleotide (Page 11 Line 30-Page 12, Line 5; Page 17, Line 30-Page 18, Line 5, for example).

Regarding Claim 2, Wang et al. disclose initial RNA samples as mRNA (Page 4, Line 2, for example).

Regarding Claim 4, Wang et al. disclose polyadenylated mRNA molecules (Figure 1, for example).

Regarding Claim 5, Wang et al. disclose tumor cells (Page 14, Lines 8-11).

Regarding Claims 6 and 7, Wang et al. discloses first oligonucleotides comprising a third "arbitrary" (i.e. random) primer sequence ranging from 14-40 oligonucleotides (Page 5, Line 29-Page 6, Line 3).

Regarding Claims 8 and 9, Wang et al. disclose Taq polymerase activities (Page 9, Line 10).

Regarding Claim 31, Wang et al. discloses a T7 promoter region (Figure 1, for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 10-13, 15-19, 21-24, 26-30, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 99/25873).

Regarding Claim 10, the disclosure of Wang et al. pertinent to the independent methods set forth in Claim 1 have been outlined in the above rejections. The instant claim sets forth a method wherein additional cDNA templates are produced by the priming of the amplified RNA (i.e. annealing said aRNA to a third oligonucleotide comprising a primer region).

It is noted, as highlighted in the above rejections, that Wang et al. disclose transcribing said cDNA templates with an RNA polymerase capable of initiating transcription via said promoter region to produce amplified RNA (aRNA) containing sequences of said target polynucleotide (Page 11 Line 30-Page 12, Line 5; Page 17, Line 30-Page 18, Line 5, for example). Wang et al. further disclose that one way of

producing cDNA from the resultant aRNA is to prime the aRNA with random primers under conditions sufficient enough o produce primer extension product (Page 14, Lines 22-24).

Wang et al. do not specifically disclose the priming of aRNA with primers comprising the equivalent structural concept of the primers used in the first polymerase reaction, however, Wang et al. disclose that following the production of double-stranded cDNA from initial mRNA, the double-stranded cDNA is then amplified with a primer (i.e. a third oligonucleotide) (Page 8, Lines 19-24, for example). Furthermore, Wang et al. disclose the primer (i.e. the third oligonucleotide) as a single primer *complementary to at least a portion of the 3' terminus of known but arbitrary sequence* of the template DNA (Page 8, Lines 29-31). This disclosure constitutes the production of additional double-stranded DNA templates (Figure 1B, for example). Wang et al. further disclose the additional amplification cycles (i.e. a second round) of the additional double-stranded DNA templates (Page 12, Line 6-Page 13, Line 17) and subsequent transcription into aRNA (Page 13, Lines 18-29). It is noted that Wang et al. highlight that additional amplification reactions, as outlined above, are beneficial to one beginning with a small population of mRNA (Page 13, Lines 29-32).

Based on the combined components of the Wang et al. disclosure, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing a method of preparing amplified RNA by the forming of double-stranded cDNA templates from initial mRNA, as outlined in the above rejections, further comprising: a) the preparation of additional double-stranded DNA templates by the

priming of aRNA with primers comprising the equivalent structural concept of the primers used in the initial polymerase reaction, and b) subsequent transcription into additional aRNA. It would have been obvious to one of ordinary skill in the art at the time of invention to, instead of produce additional cDNA templates from the initial cDNA templates, produce additional cDNA templates from the aRNA transcribed from the initial cDNA templates. The motivation to do so, provided by Wang et al., would have been to produce a large amount of amplified aRNA from a small initial population of initial mRNA through the additional rounds or amplification. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

Regarding Claims 11-13, Wang et al. discloses first oligonucleotides comprising a third "arbitrary" (i.e. random) primer sequence ranging from 14-40 oligonucleotides (Page 5, Line 29-Page 6, Line 3).

Regarding Claim 14, Wang et al. disclose Taq polymerase activities (Page 9, Line 10).

Regarding Claims 15 and 16, Wang et al. disclose the primer (i.e. the third oligonucleotide) as a single primer *complementary to at least a portion of the 3' terminus of known but arbitrary sequence* of the template DNA (Page 8, Lines 29-31).

Regarding Claim 17, please refer to the rejection of Claim 10 above.

Regarding Claim 19, Wang et al. disclose initial RNA samples as mRNA (Page 4, Line 2, for example).

Regarding Claim 21, Wang et al. disclose polyadenylated mRNA molecules (Figure 1, for example).

Regarding Claim 22, Wang et al. disclose tumor cells (Page 14, Lines 8-11).

Regarding Claim 23, 24, and 26-28, please refer to the rejection of Claims 11-13 above.

Regarding Claims 29 and 30, please refer to the rejection of Claim s15 and 16 above.

Regarding Claim 32, Wang et al. disclose T3 and SP6 promoter regions (Page 5, Lines 26-28).

Regarding Claim 33, Wang et al. discloses a T7 promoter region (Figure 1, for example).

2. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 99/25873) in view of Hyman (U.S. 5,602,000).

Regarding Claim 18, the methods of Wang et al. have been outlined in the above rejections. Wang et al. do not specifically disclose formation of additional double stranded DNA templates from aRNA further comprising the degradation of unused primers with exonuclease activity.

Hyman discloses methods for enzymatic synthesis of oligonucleotides (Columns 7 and 8, for example) further comprising degrading unused primers with exonuclease activity (Column 8, Lines 12-55, for example). Hyman further discloses the application

of an exonuclease to degrade any oligonucleotide primer which was not extended (i.e. not used) is a useful improvement in the context of any method for synthesizing an oligonucleotide (Column 21, Lines 9-12).

Based on the combined disclosures of Wang et al. and Hyman, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing a method for preparing amplified RNA comprising formation of additional double stranded DNA templates from aRNA, further comprising the degradation of unused primers with exonuclease activity. One of one of ordinary skill in the art at the time of invention would have recognized the useful improvement in the context of the method for synthesizing further DNA templates. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

3. Claims 3 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 99/25873) in view of Finke et al. (an Improved strategy and a Useful Housekeeping Gene for RNA Analysis from Formalin-Fixed, Paraffin-Embedded Tissues by PCR)" BioTechniques. 1993. Vol. 14, No. 3: Pages 448-453).

Regarding Claims 2 and 20, the methods of Wang et al. have been outlined in the above rejections. Wang et al. do not specifically disclose an formalin-fixed paraffin-embedded (FFPE) derived RNA sample.

Finke et al. disclose RNA extraction from FFPE cells further comprising cDNA synthesis and amplification (Pages 449, 450, Materials and Methods). They further disclose that their approach enabled the isolation of pure RNA, instead of a mixture of nucleic acids (Page 452, Column 2, Paragraph 3).

Based on the combined disclosures of Wang et al. and Finke et al., one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing a method of preparing amplified RNA further comprising methods of RNA extraction from FFPE cells, such as the methods of Finke et al. The motivation to do so, provided by Finke et al., would have been to enable the isolation of pure RNA, instead of a mixture of nucleic acids. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

4. Claims 14 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 99/25873) in view of Barnes ("The fidelity of Taq polymerase catalyzing PCR is improved by an N-terminal deletion" Gene. 1992. Volume 112: Pages 29-35).

Regarding Claims 14 and 25, the methods of Wang et al. have been outlined in the above rejections. Wang et al. do not specifically disclose DNA-dependent DNA polymerase activity comprising exonuclease deficient Klenow and Taq polymerase activities.

Barnes discloses the use of KlenTaq DNA polymerase, defined as a Taq analog of the Klenow fragment (Figure 1, Methods, Enzymes), in PCR reactions (Figure 1, Methods, PCR Reactions). Barnes further discloses that the enzyme was purified from wt *E. coli* cells which were induced to express the C-terminal portion of an artificial gene for Taq polymerase (i.e. Taq polymerase activity), further comprising a deletion of 235 codons containing homology to and coding for activity similar to the 5'-3' exonuclease activity of DNA polymerase I (i.e. exonuclease deficient Klenow activity) (Figure 1, Methods, Enzymes). Barnes further discloses results that indicate the KlenTaq DNA polymerase has a lower error rate (i.e. higher fidelity) than that of Taq polymerase (i.e. AmpliTaq) (Table 2; Page 33 Column 2, Paragraph 3, for example).

Based on the combined disclosures of Wang et al. and Barnes, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing a method for preparing amplified RNA comprising formation of additional double stranded DNA templates from aRNA, further comprising the use of DNA-dependent DNA polymerase activity comprising exonuclease deficient Klenow and Taq polymerase activities. The motivation to do so, provided by the results of Barnes, would have been to improve the fidelity of the polymerase reaction of double stranded DNA templates. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

Conclusion

No claims are allowed. No claims are free of the prior art.

U.S. 5,932,451 (Wang et al.) is made prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10/26/05

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AU 1637

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PRIMARY EXAMINER

10/27/05